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Thermal effects on transport in the resting mammary glands

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ABSTRACT

The increased number of women diagnosed with breast cancer in industrialized countries is raising the awareness of possible factors influencing this occurrence. The present work is based on a multi-layer transport model to analyze the concentration of toxins present in the breast ducts. The multi-layer model presented describes the transport of caffeine, cimetidine, aspirin and nicotine during the resting mammary gland period. Additionally, the dermal transport of drugs such as nicotine and aspirin into the resting mammary gland is analyzed. In a unique approach we also present the impact of introducing an external heat flux at the boundaries to increase the diffusion of these particles into the breast ducts. Our model predicts the movement of toxins and/or drugs within the resting mammary glands.

1. Introduction

Scientific Research has shown evidence of the relationship between exposure to toxins and the high risk of developing breast cancer [1]. Industrialized countries have higher exposure compared to non-industrialized nations. Immigration to industrialized countries and adopting a western lifestyle appears to increase the risk of developing breast cancer due to food additives or contaminants present in the diet and a higher exposure to environmental pollutants [1–4]. Less than ten percent of the carcinogens we are exposed to have been tested and new chemicals are constantly found every year [5]. Tougher regulations from the United States have helped reduce breast cancer rates. Lately, most of the chemicals we are exposed to are being banned or controlled such as polycyclic aromatic hydrocarbons (PAHs), second hand smoke and other air pollutants. The impact of these regulations can be significant in reducing breast cancer risk [1].

Compared to men, women have a higher presence of toxins stored in the adipose tissue [1]. This has been corroborated through tissue and breast fluid sampling done in women, in which traces of carcinogens have been found [6]. Testing done on young girls and infants also has shown detectable levels of toxins caused by the early exposure to chemicals through the maternal serum, placenta and breast milk [1]. Timing plays a key role in the environmental impact and the increased risk of breast cancer, research has shown that early exposure during breast development from prenatal to puberty increases the risk compared to late exposure [7].

Breast cancer diagnoses are increasing annually in the United States. Most of the cases develop in the ductal epithelium layers [8]. Women with abnormal epithelial cells in the mammary gland have a higher risk of developing breast cancer [9]. The development of breast cancer due to this abnormal growth is linked to morphological changes in the duct lining [9]. The type of breast cancer where malignant cells are confined in the ductal epithelium is called Ductal Carcinoma in Situ (DCIS) [10]. Less than half of the patients diagnosed with DCIS will develop invasive cancer [10]. A hypothesis for the development of breast cancer in the ductal epithelium is the accumulation of toxins in the area causing a carcinogenic microenvironment that would eventually disrupt cells [11]. A promising approach to detect the conditions of the epithelial cells lining the ducts is to test the breast fluids through minimally invasive methods.

To minimize the invasiveness clinicians are turning their attention to ductal lavage. Ductal lavage allows them to collect epithelial cells for cytologic evaluation [9]. Intraductal lavage also gives clinicians a chance to diagnose, treat and analyze DCIS [12]. An investigation of breast fluids in the ducts could detect the presence of breast cancer [13]. Nipple aspiration technique has also proven the potential to examine the conditions of the fluid. Experimental analysis done in a cohort of women demonstrated a relationship between cytological epithelial in Nipple Aspirate Fluid (NAF) and breast cancer incidence [14]. Detection of abnormal epithelial cells after performing NAF has shown a strong relationship with breast

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Nomenclature

C	concentration [mol/m^3]
S	Source [mol/m^3 s]
ε	porosity [1]
D	diffusion [m^2/s]
J	flux [mol/m^2 s]
T	temperature [K]
K_B	Boltzmann constant [kg m^2/s^2 K]
η	viscosity [Pa s]
r	radius [m]
ρ	density [kg/m^3]
c_p	heat capacity [J/kg K]
K	thermal conductivity [W/m K]
Q	heat source [W/m^3]
ω	blood perfusion rate [1/s]
q	heat flux [W/m^2]

Subscripts

B	blood
BIO	biological
MET	metabolic

cancer [9]. In the case of Ductal Carcinoma in Situ, being able to locally treat the cancer by introducing therapies through the nipple in order to reach the ductal epithelium will improve the chances of avoiding mastectomy, this technique could also be useful for drug delivery therapies [15].

In a Pre-surgery study done by Mahoney et al. they corroborated the feasibility of instilling localized therapies in the breast ductal system [10]. Different therapies are utilized to eradicate breast tumors. A useful technique is the utilization of heat sources to focus a direct heat flux on the breast cancerous site. The heat sources commonly used are ultrasound, laser-induced heat or radio wave radiation [16]. Hyperthermia in cancer treatment facilitates drug delivery, tumor eradication and it could eventually cause tumor regression if nanotubes are introduced along with thermal therapy [17,18]. The utilization of heat to treat superficial tumors was described more than 5 millenniums ago in an Egyptian papyrus [19]. In current times the application of heat has proven to be an effective method combined with radiation to control breast cancer recurrences on the long term basis [19].

Drugs and toxins can be introduced into the bloodstream through dermal patches, ingestion or injection among other methods. Several publications have demonstrated the significant effect increasing the temperature has on the properties of the layers. As the temperature rises, there is an increase in the permeability affecting directly the diffusion coefficient causing an increase in drug transport [20–23]. A better knowledge of the combination of drug therapies and hyperthermia is needed to analyze the new technologies to treat breast cancer. The aim of this research is the development of a comprehensive multi-layer mass transfer model of the resting mammary glands. Our main focus is in the breast ductal area where most of the cancer develops. Our computational model will provide a quantitative and qualitative analysis of the transport of toxins into the ducts and a unique thermal analysis is also discussed in this paper. The utilization of computational models to predict and analyze the transport in the mammary glands and arteries has been established previously by our research group [21,24–28]. Other research groups have also stated the importance of analyzing mathematically drug delivery [29–31].

2. Formulation

2.1. Multi-layer model

Experimental procedures done in the resting human mammary gland to detect toxicity levels are challenging and invasive [10,11]. Considering these limitations, research has shown that ductal lavage could provide an assessment of the breast cells conditions without being too invasive. In this work we present a theoretical approach to analyze the transport in the mammary glands. A multi-layer model is proposed considering the transport of toxins in the skin and in the bloodstream. The present work takes into consideration the particle size and properties of the layers. The transport takes into consideration the properties of each of the layers. The movement of the particles across the layers occurs by diffusion, it can be passive or by facilitated diffusion. In this case the facilitated diffusion utilizes heat to improve the transport of particles into the breast ducts. In the passive or free diffusion the movements occurs due to the high to low concentration gradient. All the layers with the exception of the breast duct cavities are acting as diffusion barriers for the particles. The dimensions and properties of the layers utilized on the simulations are shown in Tables 1–3.

The present work takes into consideration the particle size and properties of the layers. These properties affect the ratio of toxins that are able to reach the breast fluid. Our work demonstrates how the toxins enter various layers over a determined period of time making it physiologically pertinent for drug delivery. Some limitations do exist for our parameter estimation due to the invasiveness of developing experimental work in the breast tissue in order to estimate diffusion coefficients. For this reason, the diffusion coefficients for different layers were obtained using the Stokes–Einstein equation [24]. The Stokes–Einstein relationship has proven to be useful to estimate the diffusion coefficients of proteins, sugar and other small molecules in prior works [24,32–38].

2.2. Passive diffusion of caffeine, cimetidine, aspirin and nicotine into the breast ducts

The caffeine, cimetidine and aspirin transport mechanism initiates with the intake of these drugs as medication or in beverages and food. The substances enter the bloodstream gradually until they reach the peak concentration in the blood and start showing traces in the breast ducts that can be detected after performing a ductal lavage procedure [10–12]. Caffeine, aspirin, cimetidine and

Table 1
Solute properties.

		References
Caffeine particle		
Particle radius	3.7×10^{-10} [m]	[24]
Molecular weight	194.1 [g]	
Cimetidine particle		
Particle radius	5.5×10^{-10} [m]	[24]
Molecular weight	252.3 [g]	
Nicotine		
Particle radius	3.2×10^{-14} [m]	[24,60]
Molecular weight	162.2 [g]	
Aspirin		
Particle radius	2.2×10^{-10} [m]	[24,61]
Molecular weight	180.1 [g]	